Clinical Toxicology

Acknowledgment

Perfection is only for GOD. What we do is to follow HIS steps & try to praise HIS name in our lives.

Toxicology is beautiful but difficult!!! So we tried to simplify it in the form of tables to be easier for study.

These tables are the fruit of co-operations of **Dr.Didi** & **Dr.Dondon** who did extra-ordinary effort in writing these tables on the computer.

Also we would like to thank **Dr.Sara** for her great handmade tables that were the light that led us in the dark road of toxicology.

Finally we hope that you find these notes valuable & worth reading.

Please pray for us.

	Barbiturates	Benzodiazepines	Meprobamate
Uses	Main actions 1. Hypnotics (except *thiopental*) 2. Antiepileptic (*phenobarbital*) 3. Induction of anesthesia (*thiopental*) Mixed with other medications 1. Sympathatomimetics (**Anticold**) 2. Theophylline (**Antiasthmatic**) 3. Ergotamine(**Antimigraine**) 4. Phenytoin (**Antepileptic** synergistic effect) 5. **Antispasmodics** & **Antipyretics**	1. Sedatives 2. Anxiolytics (Minor tranquilizer) 3. Hypnotics 4. Muscle relaxants 5. Antiepileptic 6. Anesthetics	1. Minor Tranquilizer (anxiolytic) 2. Muscle relaxant
Metabolism	**Long acting** → minimally metabolized in liver & excreted *unchanged* in urine → longer duration of action. **Short acting** → highly metabolized in liver & only *metabolites* will appear in urine.		• Lipophilic → absorption is delayed (peak 4-6 hours) • Forms ***concretions*** in stomach → further delaying its absorption • Fluctuations of absorption → fluctuations of clinical picture • Action persists for several days
Pathophysiology	• BBI bind to **GABA_A** receptor-ionophore complex → increase ***duration*** of opening of Cl^- channels → potentiate & prolong the inhibitory action of GABA → inhibition of neuronal depolarization. • **Direct GABA mimetic effect** As a result of these two mechanisms: 1. Sedation & hypnosis 2. Anesthesia 3. Depression of brain stem centers a) RC → **RD** b) VMC → **hypotension**	They act on **GABA_b** receptors → reduce potential difference across cell membrane → block cell ability to conduct nerve impulses	
Mode of toxicity	1. **Overdose** by dependant subjects 2. **Suicide** 3. **Accidental** as in children or BBI automatism Onset → *15 min* in short acting & *1-2 hours* in long acting	1. **Overdose** 2. **Suicide** 3. **Accidental** in elderly with low tolerance to CNS depressants 4. **Criminal** to facilitate robbery & rape	
Clinical Picture	**Mild to Moderate Poisoning** **CNS** • Confusion, slurred speech, ataxia & memory disturbances • Decreased deep tendon reflexes. **GIT** → decreased bowel sounds **Severe Poisoning** A] Coma (Major Sign) • Grading is correlated with blood level of BBI	**Adverse effects of therapeutic doses** • Confusion, slurred speech, ataxia & memory disturbances • Nystagmus & postural hypotension **Paradoxical** • Hallucinations • Depression • Hostility & aggressive behavior • Paranoid reactions	**CNS** Depression as BBI Hallucinations & confusion on awakening **CVS** • Small doses → **hypotension** due to relative hypovolaemia • Large doses → **cardiogenic shock with cardiogenic pulmonary**

	B] Respiratory Depression - It leads to hypoventilation & Apnea - May be of rapid onset (1/2 hour) → *fatal* if the patient is *late in reaching the hospital.* **C] Hypotension** - Especially with *short acting* BBI - *Reversible* unless complicated by shock (due to prolonged hypoxia or delayed CPR) **D] Hypothermia** **Complications** **A] Mendelson's syndrome** - Deeply comatose patients → spontaneous vomiting → **regurgitation** of acidic gastric content into lungs → excessive destruction of alveolar membranes. - It leads to **ARDS & NCPE** **B] Rhabdomyolysis** - ***Ischemic lysis*** of compressed muscles & overlying skin in deep prolonged coma. **C] Cutaneous Blisters** - Bullae found on hands, buttocks & knees **D] Respiratory Arrest** - It leads to ***hypoxic encephalopathy*** → irreversible brain damage → death. **E] Renal insufficiency** - Due to ***renal hypoperfusion*** (hypotension, severe dehydration or shock) - BBI are ***not nephrotoxic***	**Toxic presentation** **A] Coma** **B] Respiratory Depression** **C] Hypotension** **D] Hypothermia** **E] Hypotonia**	**edema** due to depression of myocardial contractility - **Arrhythmias** ***i.e.*** *Same as BBI + cardiogenic shock & arrhythmias*
Investigations	**A] ABG** (hypoxia, metabolic acidosis) **B] Electrolytes & glucose** **C] Renal profile** (BUN, creatinine) **D] Serum barbiturate concentrations** - To determine treatment & its efficacy - ***Gas chromatography*** or ***immunoassay*** - For *phenobarbital* **E] Urine drug screen** - ***Thin layer chromatography*** - To detect poisoning by *other drugs*		

<table>
<tr>
<td>**Treatment**</td>
<td>
Emergency
ABCD
Elimination
A] Emesis → if patient is *conscious* & *vital signs are stable*
B] Lavage + ETT → greatest benefit in *1st 6 hours* but *delayed lavage can be done* as deep coma is associated with *sluggish bowel movements & gastric emptying*
C] Activated Charcoal → although MDAC increases efficacy of adsorption but *may be more harmful especially if ileus or intestinal atony are present*
Enhancement of Excretion
<table>
<tr><th>FAD</th><th>HD</th><th>Haemofiltration</th></tr>
<tr>
<td>• Long acting BBI
• Rhabdomyolysis
• CI in
1. CHF
2. Shock
3. Pulm.Edema
4. ARDS
5. RF
• Of no value in ***intermediate or short acting BBI***</td>
<td>• 4-6 times more effective.
• Acute renal failure
• Not useful in ***short acting BBI***</td>
<td>• More effective than HD
• Heart failure with or without pulmonary edema or renal insufficiency</td>
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Supportive Measures
A] Pulmonary complications
B] Rhabdomyolysis (IV fluids + $NaHCO_3$)
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<td>
Elimination
As barbiturates
FAD & HD aren't useful
Antidote
• Flumazenil 1-2 mg IV *slowly under monitoring*
• Non-specific reversible antagonist for BZDs acting on GABA receptors
• It reverses coma & amnesia
• Indications
1. **BZDs** → coma is reversed in minutes
2. **Zopiclone intoxication** → RD is reversed
• Contraindications
1. **BZDs dependence**
2. Poisoning by drugs precipitating seizures as **anti-depressants & anti-asthmatics**
Supportive Measures
</td>
<td>
Elimination
A] Emesis with syrup Ipecac
B] Lavage
• Can be repeated several times over the first few days especially if ***coma is prolonged or clinical picture is fluctuating***
C] Activated Charcoal → MDAC is more beneficial
Enhancement of excretion
A] Hemoperfusion (lipophilic drug)
B] Hemodialysis → less effective
Supportive treatment
A] Care of **coma**
B] **IV fluids for hypotension**
C] **Inotropics** (Dopamine & Dobutamine) for cardiogenic shock especially with high CVP
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	Antipsychotics (Neuroleptics)	**Antidepressants (TCA)**	**SSRIs**	**Lithium**	**Phenytoin (Diphenyl hydantoin)**	**Carbamazepine (Tegretol)**
Members	Eight different classes: 1. Phenothiazines 2. Butyterophenone 3. Thioxanthene	Amitriptyline Imipramine	1. Fluoxetine 2. Sertraline 3. Paroxtine 4. Fluvoxamine			
Uses	1. Psychosis 2. Sedation 3. Drug-induced hallucinations 4. Antiemetics	1. Depression 2. Enuresis		1. Acute mania 2. Manic depressive disorder	1. Anticonvulsant 2. Status epilepticus 3. Antiarrhythmic *especially digoxin induced.*	1- Trigeminal Neuralgia 2- Pharyngeal Neuralgia 3- Antiepileptic (except in absence of seizures) 4- Manic depressive disorder (when Li isn't effective) 5- Alcohol withdrawal
Mode of toxicity	1. Accidental	2.Suicidal		**Pharmacokinetics** - **Rapid absorption** - **Delayed tissue distribution** → serum levels after single acute overdose *don't reflect the biologically active intracellular Li^+* - **Narrow therapeutic index** - Kidney handles Li & Na in same manner - They pass freely in GF & reabsorbed in PT - Toxicity occurs due to; ✓ **Dehydration, HF & RF** → due to decreased GFR ✓ **Diuretics** → due to Na depletion ✓ **Increased Na & water reabsorption**	**Pharmacokinetics** - **95%** bound to PP - **95%** metabolized in liver - TI is very narrow → *frequent therapeutic drug monitoring is essential*	**Pharmacokinetics** - **75%** bound to plasma proteins - **Hepatic** metabolism - *Delayed absorption* → delayed signs of toxicity: ✓ **Anticholinergic action** → decreased GIT motility ✓ **Concretions** - **Strong enterohepatic circulation** **Pathophysiology** - Decrease ***Na conduction*** across nerve cell membrane → ***reduce cAMP & rate of firing of neurons*** - ***Elevation of 5HT*** & ***decrease turnover of GABA***
Pathophysiology	**Receptor Blockade** 1. *Dopamine Rs* (Limbic system, BG, hypothalamus) 2. *Alpha Rs* 3. *Muscarinic Rs* 4. *H_1 Rs* **CVS Effects** **A] Hypotension** - Peripheral VD - Depression of central VM reflex - Direct myocardial depression **B] Quinidine action** - Impaired conduction - Depressed contractility **C] Arrhythmia** (**V & SV**) **D] ECG** - Prolonged PR & QT interval - Widening of QRS complex - T wave abnormalities ***NB*** *CVS toxicity of phenothiazines can occur during therapeutic use & after overdose. They are dose related & reversible.*	**Receptor Blockade** As antipsychotics but no D Rs blockade **CVS Effects** **A] Hypotension** - Peripheral VD - Increased capillary permeability - Direct myocardial depression **B] Quinidine action** **C] Arrhythmia** **Inhibition of Neurotransmitter Reuptake** NE, 5HT or both.	**No receptor blockade** **No quinidine like action** **Inhibition of reuptake of serotonin**			

Acute toxicity	**CNS Manifestations** 1-**Depression** (RD & Coma) 2-**Convulsions** 3-Extrapyramidal • **Acute dystonia** → spasm of ms of face , neck *(torticollis)* & back *(opisthotonos)* • **Parkinsonism** → mask face, rigidity & static tremors 4-**Hypothermia** **CVS Manifestations** 1-**Hypotension** 2-**Sinus tachycardia** (reflex or M blockade) 3-**Conduction abnormalities** 4-**Arrhythmia** (PMVC, V.tachycardia or V.fibrillation) **Anticholinergic effects** 1-**Decreased intestinal motility** & **urine retention** 2-**Dry mouth** & **blurred vision** 3-**Sinus tachycardia** **Eye effects** **Miosis** (although anticholinergic effect) **Neuroleptic malignant syndrome** • Rare life-threatening • **Idiosyncrasy** • Not due to overdose • Occurs **early** in the course of ttt or soon **after change** in dose • May appear at **any time** during therapy • Manifestations ✓Muscle rigidity → increased CPK level & myoglobinuria ✓Hyperthermia ✓Stupor or coma ✓HMR > 20%	**CNS Manifestations** • **(+)** → agitation & seizures • Followed by **depression** → delirium, confusion & coma. **Anticholinergic effect** Same as antipsychotics plus; • Dilated pupils • Dry skin • Constipal hyperthermia **CVS Manifestations** Exactly as antipsychotics → ***Cardiogenic pulmonary edema***	**CNS manifestations** **Depression;** • Drowsiness • Ataxia **Stimulation;** • Anxiety • Tremors • Convulsion **CVS manifestations** **A] Tachycardia** **B] Junctional arrhythmia** **C] ECG changes;** • Prolonged QT interval • Depression of ST segment **GIT manifestation** NVD *The previous manifestations are called* ***serotonin syndrome***	**CNS manifestations** **Mild toxicity;** • Confusion • Ataxia • Tremors • *Exaggerated reflexes* **Severe toxicity;** • Coma • Convulsions **CVS manifestations** • Arrhythmia **GIT manifestation** NVD **Renal manifestations** • Polyuria • Polydipsia • DI • RF	**Oral Toxicity** **1] CNS depression** • Nystagmus • Cerebellar ataxia • Drowsiness • Coma **2] CNS stimulation** • Convulsions **3] GIT irritation** **4] Hyperglycemia** due to (-) of insulin release **IV Toxicity** **1] Hypotension** **2] Myocardial depression** • Depression of SAN • Prolongation of PR interval ***NB*** *It should be given slowly (maximum rate of 50mg/min) & the patients BP & ECG should be observed*	**CNS Manifestations** • Depression (RD & Coma) **CVS Manifestations** 1-**Hypotension** 2-**Myocardial depression** → bradycardia 3-**Conduction abnormalities** → 1st degree or even complete HB **Anticholinergic effects** 1-**Sinus tachycardia** 2-**Seizures** 3-Ataxia & Nystagmus 4-Mydriasis 5-Disorientation **In Children** Higher incidence of: 1-Dystonia 2-Choreoathetosis 3-Seizures Lower incidence of: 1-ECG changes ***DD*** *TCA & other drugs with anticholinergic actions*
Chronic toxicity	1-***C***holestatic hepatitis 2-***H***yperprolactinemia in females 3-Ext***r***apyramidal manifestations 4-Allergic dermatitis & ph***o***tosensitivity 5-Loss of l***i***bido, ***i***mpotence & ***i***nfertility in males				1-**Nystagmus, ataxia & drowsiness** 2-**GIT irritation** 3-**Seizures** 4-**Dystonia** 5-**Gingival hyperplasia**	1- **Nystagmus, ataxia, drowsiness & slurred speech**. 2- **GIT irritation** 3- **Dystonia & Myoclonus** 4- Mild transient

					(20% of patients) 6- **Osteomalacia** (disturbed vitamin D metabolism) 7- **Cleft palate & lips** (congenital)	***leucopenia*** 5- Mild elevation of liver enzymes but ***fatal hepatic toxicity may occur*** 6- **Cardiac conduction disturbances** 7- Hypersensitivity (***from rash to cutaneous vasculitis***)
Investigations	1- ABG 2- ECG 3- Toxicological screening test	Same as antipsychotics plus; • Serum drug level if diagnosis is unclear	1- ECG 2- Urine toxicological screening test	1- ECG 2- Serum Li level (therapeutic level ***0.4-1.3 mEq/L***) 3- Renal functions	1- ECG 2- Serum level monitoring (therapeutic level ***10-20 µg/ml***)	1- ECG 2- Serum level monitoring (therapeutic level 4-***12 µg/L***)
Treatment	**Emergency Measures** ABCDs **Elimination** • Emesis • GL (can be done several hours due to decreased intestinal motility) • AC **Symptomatic Treatment** **A] Hypotension** → IV fluids & vasopressor as NE **B] Arrhythmia** → phenytoin, lidocaine or DC shock **C] Acute dystonia** a) Diphenhydramine (antihistaminic) b) Benztropine (Anticholinergic which reduces ms rigidity) c) Diazepam **D] Parkinsonism** → antiparkinsonian agents **E] Neuroleptic malignant syndrome** → *ms relaxant* (dantrolene), *bromocriptine* (dopamine agonist), *cool the patient* & *diazepam*	**Emergency Measures** ABCDs **Elimination** • GL (can be done several hours due to anticholinergic effect) • MDAC **Alkalinization of Serum** Indications • CVS effects • Correct acidosis Mechanism • 1 meEq/kg $NaHCO_3$ bolus over several minutes → repeated doses or drip if needed **Symptomatic ttt** **A] Hypotension** → IV fluids & vasopressor as NE **B] HB** → pacemaker for 3rd degree **C] Arrhythmia** → Lidocaine & DC shock **D] Hyperthermia** → cool the patient ***NB** avoid physostigmine, verapamil & propranolol in TCA toxicity*	**Emergency Measures** ABCDs **Elimination** **GL** followed by **AC** **Supportive treatment**	**Emergency Measures** ABCDs **Elimination** • **Emesis** or **GL** • ***AC** isn't effective* **Serum level < 4 meq/L** **A] Good Hydration** • IV infusion of ***normal saline*** • After rehydration → ***half normal saline*** till toxicity resolves. **B] Maintenance of electrolyte & fluid balance** **C] ECG monitoring** **D]Serial estimation of Li level** **Hemodialysis** Indications; 1- **Severe toxicity** (coma, convulsions & arrhythmia) 2- **Serum level > 4 meq/L** ***NB** Slow distribution of Li may account for delayed improvement.*	**Emergency Measures** ABCDs **Elimination** 1- Emesis 2- GL 3- MDAC (due to prolonged absorption) **Symptomatic ttt** Treatment of arrhythmia Chronic intoxication 1- Stop the drug 2- Monitor serum level 3- Supportive measures	**Emergency Measures** ABCDs **Elimination** 1- Emesis 2- GL 3- MDAC (due to concretions) **Symptomatic ttt** • Cardiac monitoring & treatment of arrhythmia • ***Convulsions are treated by BZDs*** Chronic intoxication 1- Stop the drug 2- Monitor serum level 3- Supportive measures

	Naphthalene	Coumarins (Warfarin)	Strychnine	Zinc phosphide
Uses	1- Moth repellent 2- Toilet bowel deodorizers	Rodenticide	1- Rodenticide 2- Aphrodisiac. 3- Appetizer.	Rodenticide
Source	Coal tar ***NB** now it contains para-dichlorobenzene (less toxic)*		Hard seeds of Strychnos Nux Vomica (contains also brucine)	
Pathophysiology	- Its metabolite **alpha naphthoquinone** cause **RBCs hemolysis** by acting as an oxidative agent. - RBCs can't meet O_2 demand due to oxidative deamination of Hb → hemolysis - This occurs in patients with **G6PD deficiency** rapidly & with smaller doses	- Depress **hepatic synthesis of vitamin K dependant clotting factors** (1972) especially prothrombin (factor II). - **Increase permeability of all capillaries** in the body. - As a result → **widespread internal hemorrhage**	- It acts by **blocking the glycine receptors competitively.** - Glycine is a **postsynaptic inhibitory** neurotransmitter in the brain & spinal cord - So any **slight sensory stimulation may induce convulsions.**	- On its contact with water or dilute acids (in stomach) →**phosphine gas** is liberated - Phosphine gas inhibits **cytochrome oxidase** enzyme → **(-) of aerobic metabolism** - This leads to **obligatory anaerobic metabolism** → *lactic acidosis & cell death.*
Mode of toxicity	Accidental in children	1. Accidental	2. Suicidal	3. Homicidal (rare)
Route of toxicity	1-**Ingestion**. 2-**Inhalation** of its vapor in clothes or blankets by infants. 3-**Skin contamination**.	1- **Regular consumption** of contaminated food for **several days** 2- **Ingestion of** a very large amount of **rodenticide bait.**	**Ingestion**	**Ingestion**
Clinical Picture	1-**GIT** → *NVD + pain* 2-**CNS (+) then (-)** - (+) → *headache, restlessness & convulsions* - (-) → *lethargy & coma (may occur).* 3-**Optic neuritis** 4-**Hemolysis** → *hemolytic anemia & hematuria* 5-**Hepatocellular injury** *(3-5 days post ingestion)* 6-**Haemoglobinuria** → **oliguria** → **anuria**. 7-**Fever** → *flushing*. 8-**Hemolytic anemia of the newborn** if taken during pregnancy	Increase in prothrombin time after 48 hours leading to 1-Ecchymosis 2-Epistaxis 3-Gingival bleeding 4-Hematemesis 5-Hematuria	**Before Fits** NV **During Fits** 1-Stiffness of facial muscles (**trismus & Risus sardonicus**) 2-Arched back (**opisthotonus**) 3-**Convulsions of all muscles of the body** including respiratory muscles. **After Fits** 1-**Postictal depression** (the patient is exhausted & sleeps after convulsion) 2-**Lactic acidosis**. 3-**Hyperthermia.** 4-**Tachycardia** & **hypertension**. 5-**Rhabdomyolysis**	**1^{st} phase (1-24)** - GIT: **severe V & D** (garlic odor & fluorescent) → *dehydration* within mins. - CNS: lethargy, restlessness irritability **(earliest symptoms)** - **Metabolic acidosis** with *respiratory compensation.* - **Toxic cardiomyopathy** with frequent arrhythmias → *shock out of proportion to the fluid loss.* - Inhalation of fumes → **dyspnea & cough** then **pulmonary edema.** **2^{nd} phase (12-48)** - Risk of death (from CV complications or dehydration) disappear & the patient is apparently improving - It may last few hrs only or may be absent (overlapped by 1^{st} & 3^{rd} phases)

			***NB** The cause of death is respiratory failure during convulsions*	**3rd phase(36h-7days)** **A] Severe toxic hepatitis** 1. Right hypochondrial pain. 2. Enlarged tender liver, jaundice ***NB** Elevated prothrombin time & bilirubin are more confident prognostic markers for development of liver cell failure, encephalopathy & coma* **B] Renal tubular damage** → *anuria.*
Investigations	1-**CBC** (for hemolysis) 2-**Liver functions.** 3-**Kidney functions**	1-**PT** • Detectable reduction in 24-48 hrs • Maximum in 36 -72 hrs • Persisting for 1-3 weeks 2-**CBC** daily. 3-**Hb & hematocrit** every 6 hours if PT is very prolonged *to detect hidden bleeding* 4-**Urine** for hematuria.		1- **ECG** during the 1st 48 hours even if the patient appears normal 2- **ABG** , electrolytes , glucose 3- **Kidney function test** (creatinine) 4- **Liver function tests** (PT & bilirubin level)
Treatment	**Emergency measures** • ABCD • Blood transfusion if severe anemia **Elimination** 1. Inhalation → remove to fresh air & irrigate eye with copious water if affected. 2. Ingestion: • **Emesis** or **GL** • **AC** 1gm\kg **Supportive ttt** **A] TTT of hemolysis** • Urinary alkalinization • Blood transfusion • Corticosteroids (support wall of blood vessels) **B] Liver support** ***NB** IV alkaline fluid may be considered the antidote*	**Emergency measures** ABC **Elimination** **Emesis** or **GL** followed by **AC** **Phytonadione (vitamin K_1)** A] Unknown amount of poison • **Orally** (no risk for patient) • Adult → **15-25 mg** • <12 years → **5-10 mg** B]If large amounts or PT > 2 times normal (INR>2) • **IM** • Adults → **5-10 mg** • <12 years → **1-5 mg** C] If bleeding • **Infusion** (repeat in 24 hrs if still bleeding) • Adults → **10 mg** • <12 years → **5 mg** **Supportive ttt** **Bl transfusion** & **fresh frozen plasma**	**Emergency measures** ABC **Elimination** **GL**& **AC** after intubation & control of convulsions. **Supportive ttt** a. Keep patient in **quiet dark room.** b. **Anticonvulsant**. c. **Anesthesia with mechanical ventilation.** d. **Cold compresses** & **fan** for hyperthermia. e. ttt of **rhabdomyolysis** • Good hydration • Urinary alkalinzation • Control of hyperkalaemia ($NaHCO_3$, Glucose/Insulin & $Ca2^+$) • Diuretics when blood volume is expanded	**Emergency measures** • ABC • If severe dehydration → IV fluids **Elimination** **Gastric lavage** • After protection of airway from aspiration of vomitus or inhalation of phosphine gas • Should be done with ***several liters of $NaHCO_3$*** to decrease liberation of phosphine gas. **Supportive ttt** 1-**IV fluid & electrolytes.** 2-**Anti arrhythmias drugs**. 3-**Inotropics** for toxic myocarditis with shock. 4-**Liver support** (Glucose, Vitamin A & B, Albumin, Transfusion) 5-**Hemodialysis.**

	Ethyl Alcohol	**Methyl Alcohol**	**Kerosene**
Physical Properties	Clear, colorless with characteristic odor. ***Most widely abused.***	It is similar to ethyl alcohol but less expensive.	1-Low viscosity. 2-Low volatility.
Source	***Beer*** → 3-6% ***Wine*** → 10-14% } Products of fermentation ***Fortified wines*** (campari, martini & vermouth) → 22-25% ***Whisky, Brandy, Grin & Vodka*** → 40-55% *The last two are productus of distillation where alcohol is fortified*	Produced by distillation of wood	One of the petroleum distillates **hydrocarbons**
Uses	1- **Alcoholic beverages**. 2- **Sterilizing solution** (70 %) or with tincture iodine in medical uses. 3- **Solvent & vehicle** of many household and industrial products. 4- **Cosmetics products**.	Cleaner & solvent (denatured by pyridine → rosy offensive alcohol of bad taste) ***NB*** *non denatured methanol will produce the same euphoric effect as ethanol.*	Mixed with insecticides & other toxic chemicals → can be more dangerous than kerosene itself. ***NB*** *if other toxins as pesticides are present → clinical picture may by atypical to kerosene*
Mode of toxicity	1- **Overdose** in an inexperienced young adult. 2- **Chronic intoxication** from *alcohol dependence*		Mostly **accidental ingestion by children.**
Pathophysiology	**Central Effects** • Ethanol is *dose dependant CNS depressant* • It affects (-) & (+) neurotransmitters as *dopamine & serotonin*. • Effect on cortex reaches its peak while blood level is increasing • In larger quantities → (-) of medullary RC → **RF & respiratory acidosis** **Metabolic Effects** • Its metabolism affects NAD/ NADH ratio → **hypoglycemia** (decreased NAD) and **metabolic lactic acidosis** (blocking of conversion of lactic acid to glucose) • VD increases cutaneous blood flow with impaired central thermal autoregulation leads to **hypothermia** ***NB*** *Ethyl alcohol is oxidized to acetaldehyde then to acetic acid then to H_2O & CO_2 by alcohol dehydrogenase. If this enzyme is inhibited (e.g. by antabuse (disulfiram)) → accumulation of intermediate products producing their own effects*	**Kinetics** • Well absorbed from GIT, evenly distributed in whole body water including **gastric secretions**. • **Metabolized in the liver**, and excreted in the urine as toxic metabolites. **Metabolism** • **Slowly** metabolized in the liver by alcohol dehydrogenase (preferentially use ethanol) to **formaldehyde** then **formic acid** • The enzyme utilizes methanol when ethanol isn't available **Effects of Formic acid** • **Metabolic acidosis** due to its accumulation • **Lactic acidosis** due to inhibition of cytochrome oxidase → obligatory anaerobic metabolism • Local accumulation leads in CNS & optic nerve leads to **optic atrophy** & **central neurological sequelae.**	**Respiratory Tract Injury** • Low volatility & low viscosity → **aspiration** & spread of the liquid in the lung down to terminal bronchioles & alveoli • This will cause **destruction** of lining **surfactant** in the alveoli (*rather than direct parenchymal injury*) → **acute chemical pneumonitis.** **CNS toxicity** • *Indirectly* → secondary to **hypoxia** • *Direct depression* → if **large** amount. **Cardiac toxicity** • **Severe arrhythmias** (due to either *sensitization of the heart to circulating catecholamines* or *hypoxia*) → **sudden death** **GIT effects** • **Direct** local irritation **Cutaneous injury** • Due to its **irritant effects** & **fat solubility**

Clinical Picture	**Mild Toxicity** A] Higher cortical depression → release of emotions: • **Euphoria** • **Talkativeness** → becomes **noisy** B] **Conjunctival injection** C] **Increased appetite** in *non-addicts.* **Moderate Toxicity** A] Cortical & subcortical depression: • **Cerebellar Ataxia** (Staggering gait – Tremors – Slurred speech) • **Slow respiration** • **Diplopia** B] **Vomiting** & **hiccough**. C] **Cutaneous VD** → flushing & sweating → *false feeling of warmth* with *actual hypothermia.* **Severe Toxicity** Severe CNS depression → coma with: • **Hypothermia** • **Hypotonia** & **Hyporeflexia** • **Hypotension** • **Irregular acidotic breathing**	**Visual** • Blurring of vision → **blindness** (due to optic atrophy) • Ocular pain & papilloedema **Metabolic Acidosis** • **Air hunger** (rate more than depth) • Confusion , headache , weakness • **Hyperkalaemia** (if severe acidosis) → life threatening **GIT** Vomiting, abdominal cramps & **dehydration** **Neurological** **A] CNS depression** (disorientation stupor & coma) → caused by metabolic acidosis & accumulation of formic acid in CSF **B] CNS stimulation** → convulsions (serious) **C] Encephalopathy** **D] Delayed necrosis of the basal ganglia** → *spasticity* & *dyskinetic movements* **Respiratory Depression** Follows air hunger if severe acidosis & coma **Shock** **A] Cardiogenic** → due to acidosis, ischemia & hyperkalaemia-induced depression of myocardial contractility. **B] Vasoplegic** → (-) of VMC 2ry to brain edema due to local accumulation of metabolites. **C] Hypovolemic** → due to dehydration ***NB*** *Symptoms appear after a latent period of 12-36 hrs due to slow metabolism*	**Pulmonary** 1-**C**haracteristic smell of kerosene. 2-**C**ough. 3-**C**yanosis. 4-**C**hemical pneumonitis with • Intercostal retraction • Dyspnea & tachypnea • Ronchi & wheezes with decreased breath sound • Fever 5-**Bronchopneumonia** 6-**Pulmonary edema** **GIT** • NV with characteristic smell of kerosene • Diarrhea, abdominal pain & distension → less common **Neurological** • **CNS (-)** → dizziness, stupor, hyporeflexia, coma with RD • **CNS (+)** → convulsions (rarely) **Cutaneous** • Mild erythema • Dermatitis, redness, itching & inflammation may be seen. **Cardiac** • Tachycardia • Atrial & ventricular arrhythmias. **Cause of death** • In the first 24 hrs 1.**Central respiratory depression** 2.**Sudden arrhythmias** • Late in few days 1.**Secondary to bronchopneumonia** 2.**Pulmonary edema.**
Investigations	1- ABGs 2- Blood alcohol level. 3- Glucose (**hypoglycemia**) 4- Electrolytes (**High anion gap** , **high osmolarity gap**, **ketoacidosis**)	1- **ABGs** & electrolytes 2- Random blood sugar (RBS), urea 3- **Methanol blood level** (above 25 mg/dl indicate antidote & hemodialysis) 4- ECG **5- Fundus examination** & **VEP**	1-**ABGs**. 2-**ECG** monitoring. 3-**Chest X- ray**. 4-Laboratory Investigation of **toxic additives**

Treatment	**Emergency measures** ABCD **Gut decontamination & elimination** • Mild cases left undisturbed • Stupor & coma may benefit from **GL** • *AC isn't useful* • *Avoid emesis* **Thiamine 100 mg IV or IM** If coma is due to *Wernicke's encephalopathy*	**Supportive Treatment** • **ABC** • **Diazepam** for convulsion • Control acidosis (if pH<7.15) & hyperkalaemia by **slow infusion of IV bicarbonate** • **Steroids** (early for optic neuritis & late for cerebral edema) **Gut decontamination** Gastric lavage in first 24 hours. **Antidotes** **A] Ethyl alcohol** *1gm/kg* followed by *0.5mg/kg/4 hours* to maintain blood ethanol at *100 mg/dl* **B] 4-Methyl Pyrazole** *Both compete with methanol for alcohol dehydrogenase enzyme → excretion of methanol as parent compound.* **C] Folinic acid** helps oxidation of accumulated formates **Hemodialysis** Indicated if • Methanol level **> 25-30 mg/dl** • Aggressive **acidosis refractory to ttt** • Precipitation of **renal failure**	Mild cases • **No emesis or GL** for *fear of aspiration*. • Observation & follow up. Severe cases showing **CNS manifestations**, **systemic manifestations** or **combination with insecticides** **Emergency measures** ABCD **Elimination of toxin** A] Dermal exposure • **Remove** contaminated clothes • **Wash** skin with water and soap. B] Ocular exposure • Irrigation with **sterile saline** or with **tap water** C] Ingestion • In severe cases (*more than 1 ml/kg*) or dangerous additives → **GL** after introduction of cuffed endotracheal tube to prevent aspiration • **AC** is not effective & may be harm **Drug therapy** **A] Corticosteroids** for *chemical pneumonitis* (used cautiously as they may affect immunity → infection) **B] Antibiotics** → if *bacterial pneumonia*

	Lead	Mercury	Iron
Properties	• It occurs in **organic** & **inorganic** forms • It is the most common metallic poisoning • In children on organ is immune to its effects		• Very common cause of poison emergencies specially in children
Source/ Methods of exposure	**Water and food contamination** • Water from **lead pipes** or **storage tanks**. • Food grown **near factories**. • Licking **toys or paints** by *children* ***NB*** *50% of ingested dose is absorbed in children while only 10% in adults* **Inhalation** • From **motor vehicle exhaust** when leaded gasoline is used **Occupational exposure** • Lead workers, glassmakers • Scrap metal workers, plumbers • Workers in battery factories **Dermal exposure** • **Alkyl lead** easily absorbed through skin	**Elemental mercury vapor** • Dental amalgam, glass thermometers and sphygmomanometers. • **Toxicity only after inhalation**, no toxicity when swallowed (*poorly absorbed*) **Inorganic salts** • Laxatives, teething powder • **Mercuric fulminate** → *explosive* • **Mercuric Cl** → *disinfectant* **Organic mercury compounds** • Incorporated and **concentrated in aquatic food** as eating contaminated fish *due to discharge of contaminated wastes*	**Ingestion** • **Accidental** in children • It is a common because **available at home**, present in **attractive colored sugar coated preparations** • Severity depends **upon amount of elemental iron ingested**. • Amount ingested = N^{o} of tablets X percentage of elemental Fe in salt
Pathophysiology	• Disturb multiple enzyme system • Any ligand with **SH group** is a target **Hematological effects** **A] Anemia** • *Normochromic* or *hypochromic microcytic* • More in *children* • *Uncommon* in *inorganic* lead poisoning Mechanism 1. *Defective Hb synthesis* A. (-) conversion of **DALA** to **porphobilinogen** B. (-) conversion of **coproporphyrinogen III** to **protoporphyrin** C. (-) incorporation of **Fe** into **protoporphyrin** to form heme. ***NB*** • *DALA* and *Coproporphyrin* accumulate **in urine** → used as **toxicity markers** • *Protoporphyrin* accumulate **in RBCs** → **chelates zinc** • *Erythrocyte protoporphyrin*(EP) reflect **chronic lead exposure** 2. *Increased RBC fragility* • Interferes **with Na-K ATPase pump** • **Attack RBC membrane** 3. *Erythropoietin deficiency* • Due to **toxic effects on renal tubules**	1. *High affinity for SH groups* →enzyme dysfunction → **(-) choline acetyl transferase enzyme** →Ach deficiency → S/S of motor dysfunction 2. *Immune mechanism*→ **Membranous GN**, **acrodynia**	**Local effects** • **Corrosive** to GIT mucosa **Systemic effects** • Affects **internal organs** (lung, liver & heart) • Excess free Fe is a **mitochondrial toxin** → **disturbance in energy metabolism** ***NB*** *Serum levels are useful in predicting clinical coarse of the patient*

	B] Basophilic stippling of RBCs • Due to ↓ ability of RBC to get rid of RNA degradation products followed by **aggregation of ribosomes** **C] Reticulocytosis** • Response of bone marrow to anemia **D] Mild hemolysis** • Due to increased RBCs fragility **Renal effects** **A] Acute toxicity** → *direct tubular damage* (**Fanconi-like syndrome**) specially in *children* **B] Chronic toxicity** →*chronic interstitial nephritis* **C] Alters rennin-angiotensin system**→ *hypertension* **D] Alters uric acid excretion** → *hyperuricaemia* and *gout* **Nervous effects** **A] Direct effect on CNS** • *Lead encephalopathy* (specially children) • *Delayed* or reversed *development* • Permanent learning disabilities ***NB*** *Developing brain is the most risky organ to be affected* **B] DALA is neurotoxic** (interfere with GABA) **C] Chronic lead exposure** • Affects peripheral nerves(motor)→*wrist and foot drops* **Reproductive system effects** **A] Crosses the placenta** → *abortion*, *still birth*, *neuro-developmental* problems **B] ↓ sperm count & ↑number of abnormal sperms** **Bone effects** **A] (+) of hypermineralization** • This is reflected in **metaphysical and growth plate densities** ***NB Classis Lead Lines*** *on radiographs reflect bone growth arrest not deposition, their width is related to duration of exposure* **B] (-) conversion of vitamin D into the active form**		
Clinical Picture of acute toxicity	• **Uncommon** • Results from **accidental** or **suicidal ingestion** of lead oxides **GIT** • Metallic taste, anorexia & vomiting • Colic & constipation **CNS** • Encephalopathy, behavioral changes • Lethargy, fatigue • Seizures ,coma	• **Accidental** or **suicidal** ingestion of *Hg Cl* **GIT** • NV & **hematemesis** → **dehydration**, **collapse** • **Severe cramps**, **burning sensation** & metallic taste • *Re-excretion in caecum* → **dysentery** • *Re-excretion in saliva* → **stomatitis**, **gingivitis** & **increased salivation**	**Stage I (1-6 hours post ingestion)** **A] GIT irritation** • NVD & **GIT bleeding** (may be severe)→ **shock**. • Abdominal pain. • Necrosis may be severe → **perforation** and **peritonitis** **B] CNS depression** (in severe cases) → lethargy, coma

		Acute toxic GN • **Hematuria, casts** **Cause of death** • *24hrs* → **dehydration** • *1-2weeks* → **uremia**	**Stage II (Quiescent phase) up to 24 hrs** • Apparent false improvement in most cases **Stage III (12-48 hrs)** **A] Metabolic acidosis**, due to • **Hydrogen is released** on conversion of Fe^{2+} to Fe^{3+} in the blood • *Interference with Krebs cycle*→ **accumulation of organic acids** • **Shock** & **lactic acidosis** **B] Fever and leucocytosis** • Due to **invasion of damaged intestinal mucosa by bacteria** **C] Hepatic necrosis** • *Liver cell failure* → jaundice, hypoglycemia & coagulation defect **D] Renal failure** • C & D are due to deposition of excess iron *exceeding total iron binding capacity (TIBC) in soft tissue* **E] Coma and CVS collapse** **Stage IV (4-6 weeks)** • **Intestinal scarring** *with or without obstruction*
Treatment of acute toxicity	**Emergency measures** ABCD **Elimination** **Emesis** or **GL**(if ingested) **Chelation** See chronic toxicity **Symptomatic ttt** • Dehydration → **IV fluids** • Lead colic → **Ca gluconate** • Encephalopathy →**care of coma**, **convulsions** • **Mannitol** to decrease ICT	**Emergency measures** ABCD **Elimination** **Emesis** or **GL**(if ingested) **Chelation** **Penicillamine** or **BAL** (Antidotes) **Symptomatic ttt** • Dehydration → **IV fluids** • Renal failure → **hemodialysis** • **Mouth hygiene**	
Chronic toxicity	**Plumbism** 1. **Non specific** → vague body aches, anorexia, colic, constipation 2. **Blue lines on the gums** → precipitated lead sulfide due to bacterial action. 3. **Peripheral neuritis** → wrist and foot drops 4. **Optic neuritis** may occur 5. **CNS** → cognitive disturbances, headache, encephalopathy(children) 6. **Hematological** → anemia, reticulocytosis, hemolysis 7. **Renal impairment** 8. **Bony aches** and **gouty arthritis** 9. **Myocarditis**	**Mercurialism** 1. **GIT** → • Recurrent stomatitis, ptyalism (↑ salivation), gingivitis • Recurrent vomiting, diarrhea & weight loss 2. **Grey line on gums** 3. **Nervous affection** → *kinetic intention tremors* → 1st in tongue (*hesitant speech*) then hands 4. **Visual cortex affection** → contraction of visual field 5. **Psychological** → *Erythrism* • Shyness, fear & loss of self confidence • Irritability, Insomnia & mental deterioration 6. **Renal affection** → toxic GN 7. **Cutaneous affection** → dermatitis ***NB** Mode of exposure is Industrial* → ***inhalation of mercury fumes***	
Treatment of chronic toxicity	**I] Prophylactic** • Decrease exposure: masks, gloves • Periodic medical examination of workers	**I] Prophylactic (as lead)**	Treatment of ACUTE toxicity **Emergency measures** • ABCD

	II] Curative • Stop further exposure • Symptomatic *Anemia* →**blood transfusion** *Renal affection* →**hemodialysis** *Wrist and foot drop* → **splint** & **physiotherapy** • Chelation **Dimercaprol (BAL)** • Lipid soluble →cross BBB rapidly → **first chelator used in encephalopathic individuals** • Remove **IC** and **EC** lead • **IM only** (*IV cause fat embolism*) **Calcium disodium EDTA (CaNa$_2$EDTA)** • Allow **EC** lead to be **renally eliminated** • Not metabolized, few toxic effects • Once started**, should be given in full 5-day course** • **1st dose removes lead from ECF in bone**, if not followed by next dose→ **free lead will redistribute** → **neurotoxicity** • In lead encephalopathy → **give BAL first** to avoid redistribution of lead mobilized by CaNa$_2$EDTA to CNS **D-Penicillamine** • Effective **orally**, few adverse effects **Dimercaptosuccinic acid (DMSA)** • Effective oral chelator • The **best** for **children** with lead **level >45µg/dl** **Dimerval (DMPS)** • **Oral** form & **water-based parenteral** form • Antidote for **most heavy metal intoxications**	**II] Curative** • Stop further exposure • Symptomatic *Renal affection* →**hemodialysis** • Chelation → **Penicillamine** or **DMSA**	**Elimination** • **Emesis** or **GL** • *AC not used* (can't adsorb Fe) **Antidote → Deferoxamine (Desferal)** • Fe chelating agent • Excretes **Fe-deferoxamine complex** in **urine** • **Doesn't bind Fe** in *Hb*, *myoglobin* or *other Fe carrying proteins* • Indications: 1.Serum Fe **> 500µg/dl** or estimated dose **> 60mg/kg** of elemental Fe 2.**Shock** 3.**Altered mental status** 4.**Persistent GIT symptoms** 5.**Metabolic acidosis** 6.Serum Fe level **not available** with **presence of symptoms** **Symptomatic** • IV fluids • Liver support • Dialysis • Correction of acidosis
Investigations	1.**Blood level** of *Lead* → more than **30µg/dl** is abnormal *EP* → more than **50µg/dl** is abnormal 2.**CBC** *3.***Urinary DALA**, used as *screening test* 4.**Renal functions** 5.**Liver functions** 6.**Serum uric acid** 7.**X-ray on long bones** to reveal *lead lines*	1.CBC 2.Electrolytes 3.Renal function tests	1. Serum Fe (**N=80-100µg/dl**, **action level >500µg/dl**) 2. **Electrolytes** 3. **ABGs** 4. **Renal function tests** → BUN, creatinine 5. **Hepatic profile** → transaminase, bilirubin, coagulation profile 6. **X-ray abdomen to detect radiopaque shadows**

	Digitalis	Beta Blockers	Nitrates & Nitrites	Theophylline
Uses	1. Congestive heart failure 2. Atrial fibrillation	1. **Hypertension** 2. **Arrhythmia** 3. **Coronary heart diseases** 4. Management of **migraine**	1.Angina 2.Fertilizers 3.Food processing	Asthma
Source	**Digitalis purpurea** and **Digitalis lanate**. ***NB*** *Digoxin is the most commonly used digitalis preparation*	**Inorganic nitrates** 1. **Sodium nitrate** used to *preserve the color of meat* in the pickling or salting process. 2. **Silver nitrate**, used for its caustics and disinfectant properties. It is also *apply to burns to reduce infection.* 3. High concentrations occur naturally in spinach, beets, carrots, and cabbage. *The toxic nitrites form after the substance is **cooked** and then **allowed to stand at room temperature***. **Organic nitrates (antianginal drugs)** 1. **Nitroglycerin**. 2. **Isosorbide dinitrate** (Isordil, Dilatrate) **Inorganic nitrites** 1. **Amyl nitrite** used to *treat cyanide poisoning* and *to diagnose cardiac murmurs*; currently used *as drug of abuse* (street name Mama Poppers) 2. **Sodium nitrite** used for the treatment of *cyanide poisoning* in conjunction with sodium thiosulfate. *3.* **Isobutyl nitrite** is used as *room deodorizer*. It may be *abused by homosexuals.* **Organic nitrites** *1.* **Bismuth subnitrate** in contaminated well water *may be converted by intestinal bacteria to nitrite.* *2.* **Nitrates** in contaminated water in the presence of **Bacillus subtilis spores in dried milk powder** *are transformed* to **nitrites**.		Methylxanthines alkaloids Preparations Epicophylline-Theo.SR-aminophylline
Pathophysiology	**Reversible (-) of Na-K ATPase pump** • In heart → **↑intracellular Na** & **↓ intracellular K** • In skeletal ms →↑ extracellular K → **hyperkalaemia** • May **increase inotropy** in therapeutic doses due to **intracellular accumulation of Ca^{2+}** **Vagotonic effect** • **Bradycardia** & **HB** **Various Types of Arrhythmias** Due to; 1. **Prolongation** of refractory period in **AVN** 2. **Shortening** of refractory periods in **atria** &	**Negative inotropic & chronotropic effect** • ↓ adenylate cyclase enzyme → ↓ cAMP • This leads to *↓ influx of Na & Ca ions* **Membrane stabilizing effect** • **TCA or quinidine** like *depression of myocardial contractility and conduction* **CNS Depression & seizures** **Due to ↑lipid solubility**→ *↑CNS penetration of drug*	**CV Effects** • **↑ synthesis of cGMP → relaxation** of smooth muscles in **coronaries**, **peripheral arteries** and **veins → ↓cardiac preload, and output.** • Compensatory **↑in pulse rate** and **arteriolar vasoconstriction** ameliorate these effects. • At therapeutic doses neither inotropy nor chronotropy is affected significantly, but at higher doses the **myocardium** is depressed.	1-**Relaxation** of **smooth muscles** (mainly bronchial muscles) 2- (+) **CNS** 3- (+) **diuresis** 4- ↑serum **catecholamines** 5- ↑**contractility** of skeletal ms 6- ↑GIT secretions of **HCL** and **pepsin** 7- **VD** except cerebral circulation

	ventricles 3. Decrease RMP → **increase excitability** Types of Arrhythmias; 1. **Sinus rhythm** with **PVCs** (premature ventricular contractions) 2. **Sinus bradycardia** with all types of **AVN block** 3. **Junctional rhythms** (AVN is the pacemaker) and **sinus arrest** 4. **Paroxysmal atrial tachycardia** with **block** 5. **Junctional tachycardia** 6. **Ventricular tachycardia** and **VF** ***NB*** *The 1st three are the most common with digitalis toxicity*		**Methemoglobinaemia** • Ferric iron is **incapable of binding oxygen.** • Methemoglobin also causes **shift of oxygen dissociation curve to the left** → impairs unloading of oxygen to tissues. • Methemoglobin is normally present as *less than 1%* • There are two reducing mechanisms to keep this level 1. The reduction of **oxidizing compounds** 2. The reduction of **formed methemoglobin** • Reduction of Met-Hb occurs through two enzymes in RBCs; A. **NADH-dependent methemoglobin reductase system** → most active, 95% B. **NADPH-dependent methemoglobin reductase** → 5% • NADPH pathway needs 1. Cofactor **methylene blue** 2. Functioning **hexose monophosphate shunt**, which requires in its first step **G6PD**. ***NB*** *NADPH pathway is the reserve system that is accelerated in the presence of an exogenous electron carrier as methylene blue.*	
Mode of toxicity	1. **Accidental** in children 2. **Suicide** 3. **Chronic poisoning** in long standing ttt in *elderly patients* with *renal disease & cardiac diseases* due to • **Large doses of digoxin relative to age** • **Changing renal function** Concurrent **diuretic administration** may produce **hypokalaemia** & **hypomagnesaemia**		**Pharmacokinetics** • **Inorganic nitrates** are rapidly absorbed through **gastric mucosa**. **Silver nitrate** also absorbed through **skin**. • **Organic nitrates** ➢ Rapidly absorbed through **skin** and **GIT**. ➢ They undergo **first-pass hepatic metabolism** → *high doses* are needed *orally* to *saturate the liver's capacity for degradation*, so enough nitrates would *reach the circulation*. ➢ SL form has $t_{1/2}$ of 1-3 min, with peak concentration at 4-6 min. • **Inorganic nitrites** (Amyl nitrate, isobutyl nitrite) ➢ Absorbed from mucous membranes, **most rapidly by the lungs**; ➢ Inactivated by **hydrolysis**. ➢ It is **inactive** when taken orally, as it is **rapidly hydrolyzed** in the **GI tract**.	1. **Accidental** → iatrogenic or parent error *NB Serum monitoring during ttt is a must* 2. **Suicidal** ***NB*** *It has a narrow therapeutic margin* ***(10-20 µg/ml)****. Chronic patients develop at lower serum level than acute patients*

Clinical Picture	**Cardiac manifestations (the most frequent)** • Bradycardia, any degree of HB • A & V arrhythmias & palpitations • Hypotension and shock **GI symptoms (the first to evolve)** • NVD • Abdominal pain & anorexia **Visual effects** • Blurred vision • Abnormal color perception of **yellow or yellow-green halos** **Electrolytes Imbalance** • *Hyperkalaemia* → is 1^{ry} **manifestation** of **acute cardiac glycoside toxicity** and is an **early predictor** of need for **antidotal therapy** • *Hypokalaemia* in **chronic toxicity** due to concomitant use of K losing diuretic → **exacerbates chronic toxicity** **Others** • Headache, fatigue & weakness	**CV Effects** • Hypotension & bradycardia • Arrhythmias with **AV block** and **prolongation of QRS interval** • **Cardiogenic shock**, **asystole** in serious overdose **CNS Effects** • Seizures • **Coma** with **respiratory depression** or arrest **Others** • **Hypoglycemia** • **Hyperkalaemia** **Bronchospasm** *in asthmatic patients*	• The effects of depend upon 1. Form, route & dosage **2.** Cardiopulmonary status and the **total Met-Hb rather than its %.** **CV Manifestations** **A] Vasodilatation** • *Throbbing headache* & flushed face • Rapid fall in blood pressure and *cardiogenic shock* **B] Effects on Heart** • *Tachycardia* & ↑ *force of contraction* (compensatory due to hypotension) → **elevation of blood pressure** • In *severe toxicity* the heart may be *unable to respond* → **hypotension, shock** and **cardiovascular collapse**. **Effects of Methemoglobinaemia** **A] Cyanosis** • In mild cases → only on the **lips** and **mucous membranes**. • The patient may appear deeply cyanosed and yet completely asymptomatic at lower concentration. • Due to **abnormal pigment** *rather than hypoxia.* • Application of oxygen **does not improve this cyanosis** **B] Effects due to hypoxia** • S/S appear if level **> 10%** • **20-30%** → Only *mild symptoms* of headache, fatigue, & nausea • **30-45%** → **Dyspnea** on exertion and **tachycardia** • **50-70%** → **Arrhythmias**, coma, seizures, **respiratory distress**, and **lactic acidosis**. • **> 70%** → CV collapse and have a high mortality	**CVS** **A] Tachyarrhythmia** • *Sinus tachycardia* (most common) • *VF and cardiac arrest* may occur with increasing level • *All other types* may be present **B] Hypotension** in 25% overdoses (due to VD) ***N.B*** *Rapid IV injection of theophylline may lead to death due to cardiac arrhythmias, hypotension* **GIT** • NVD • Abdominal pain • **Upper GIT bleeding** **CNS** **A] Agitation, restlessness** **B] Generalized seizures** • The most concerning as **they are associated with high mortality** • Occur when serum level reaches **>80μg/ml** *(acute cases)* **>40 μg/ml** *(chronic cases)* • Prolonged seizures can contribute to **rhabdomyolysis** **C] Coma** may occur **Metabolic** **A] Hypokalaemia** (intracellular shift of K$^+$ due to increased level of catecholamines leading to activation of Na-K ATPase) **B] Hyperglycemia** **C] Metabolic acidosis**

Investigations	1-**Digoxin level** • Therapeutic blood level **0.6-2.1ng/ml** • Serious prognosis if **>15ng/ml** 2-**Electrolytes** • Hyperkalaemia or Hypokalaemia • Hypercalcemia & Hypomagnesaemia exacerbate cardiac glycoside toxicity 3-**Renal functions** • Impairment impairs elimination of glycosides 4-**ECG and continuous cardiac monitor** • Bradycardia HB, A or V tachyarrhythmia • Nonspecific *ST segment sagging* & *T wave abnormalities* are consistent with digitalis ttt *Peaked T wave* may occur in *hyperkalaemia*		1. **Serum methemoglobin level** • Concentration will be *false low* if *not* measured *rapidly*, through the *action of endogenous Met-Hb reductase* • Roughly measured by placing a *drop of blood* on *filter paper*. If blood *remains brown* compared to a control sample → **>15%.** 2. **ABGs** • **Normal PaO_2** as Met-Hb *does not interfere with diffusion of oxygen from the lungs*. • Clinical cyanosis in the presence of normal arterial PaO_2 is highly suggestive of methemoglobinaemia. 3. **Serum electrolytes**. 4. **ECG**	1-**Theophyline serum level** (N= 10-20 µg/ml) 2-Serum electrolytes especially **K^+ level** 3-Serum **glucose** 4-ABGs • **Metabolic acidosis** • **Respiratory alkalosis** due to stimulation of respiratory center 5-**ECG**
Treatment	• **Emergency measures** →ABCD • **Prevent further exposure** → stop digoxin medication • **Continuous cardiac monitoring** **Elimination** • **GL** preferred to emesis in acute digoxin toxicity • **AC** • **Cholestyramine** →interrupt enterohepatic circulation **Antidote (Digibind)** • Digoxin specific **MCA**(Fab fragments) • Dose depends on **digoxin blood level** or **amount ingested** and **body weight.** • Onset of action may take **30-60 min** • **Monitor K level** (*hypokalaemia may occur due to activation of Na-K-ATPase*) • Indications 1. Serum level **>10 ng/ml** in adults or **>5 ng/ml** in children 2. Ingestion **>10mg in adults** or >**4mg in children** 3. Hyperkalaemia **>5.5mEq/L** 4. **HB even 1st degree** 5. Life-threatening **SV or V arrhythmias**	**Emergency measures** • ABCD **GI decontamination** • *GL better than emesis* due to **rapid absorption and precipitous onset of toxicity** • Lavage is beneficial if the patient presents to the ER **within 1-2 hours** of ingestion. • **Pre-treat with atropine before lavage** **Antidote (Glucagon)** • ↑inotropic and chronotropic effects through a **non-adrenergic mechanism** • *(+) myocardial adenylate cyclase*→↑cAMP and enhanced cardiac contractility • *↑movement of Ca in myocardial cells* → ↑cardiac performance • *Doesn't contour the membrane stabilizing effect of some BB* (e,g prolongation of QRS interval)	**Emergency measures** • ABCD **GI decontamination** • **GL** followed by **AC** and a **cathartic**. **Specific Measures** **A] Methylene blue** • *First-line antidote*. • It accelerates the enzymatic reduction of methemoglobin by *NADPH-methemoglobin reductase* • The initial dose is **1-2 mg/kg IV over 5 min**. Its effects should be seen in **20 min to 1 h.** • Patients may require **repeated dosing** • **Met-Hb level** should be significantly improved **within one** hour of infusion • **High doses** of methylene blue may actually induce a **paradoxical methemoglobinaemia**. • Failure may occur in 1. **Ongoing exposure**. 2. **Sulfhemoglobinaemia** 3. Abnormal hemoglobin (i.e. **HbM**)	**Emergency measures** • ABCD **Elimination** **A] Emesis** • Better avoided as it may lead to *intractable vomiting* **B] GL** • Using large bore tube. • It may be *delayed* in case of *sustained release preparations* **C] AC** • OAC 1gm/kg • MDAC 20g/2hrs to 40g/4hrs (***NB*** *theophylline undergoes gastrointestinal dialysis*) **D] Cathartics** • Concomitant use is *more effective in decreasing serum level* ***NB** If OAC is difficult, nasogastric tube may be used.*

	6. **Hemodynamically significant bradycardia** *unresponsive to atropine* **ttt of Complications** 1. **Atropine** in bradyarrhythmia 2. **Phenytoin or Lidocaine** in V arrhythmias 3. **Mg sulfate** reverse digoxin-induced arrhythmias 4. **Cardiac pacing**(temporary pacemaker) **in serious HB** *if Fab fragments are not immediately available* 5. Life-threatening hyperkalaemia *>6.5mEq/L*→ **G + Insulin + NaHCO$_3$** **Avoid the following** 1. **Ca preparations** 2. **Cardioversion**(DC shock) to revert V arrhythmias *as resistant VF may occur* **Diuresis**, **Hemodialysis**, **Hemoperfusion** → *they don't increase clearance* due to *large volume of distribution*. They may *lead to fluid imbalance and exacerbate CHF*	- Dose→initially **IV 50-150 mcg/kg** followed by **infusion** of **1-5 mg/hr** - Beneficial effects appear **within 1 min** - Larger doses may be needed to produce the desired effect **Specific management** **A] Fluids** for hypotension **B] Atropine** - 1st line of treatment of clinically important **bradycardia and hypotension** (e.g. symptomatic patients with hypotension & confusion despite use of fluids) **C] Catecholamines** - *Epinephrine and isoproterenol* → not useful as **BB are tightly bound to β Rs** - Supra-therapeutic dose of isoproterenol to unblock the receptors → **↑myocardial oxygen demand** and **↑predisposition to arrhythmia** **D] Mg sulfate or Lidocaine** for arrhythmias	- *Contraindications* 1. **G6PD deficiency**, *if possible,* because it may *induce hemolysis* 2. **Cyanide poisoning** treated with overdose of sodium nitrate (or any other nitrites or nitrates), *as release of cyanide occurs.* **B] Exchange transfusion**, in 1. **Infants**. **2.** Patients who do not respond to methylene blue within **30 to 60 minutes.** **3.** Patients with **G6PD deficiency**. **4.** Patients with MetHb levels **> 70%.** **Symptomatic ttt** - **Atropine** for bradycardia. - **Diazepam** or **barbiturates** for seizures - **Avoid** *vasoconstrictor drugs.* **Disposition** - Rapid treatment **avoids complications of shock** (brain damage, RF, and MI). - There are **no long-term sequelae** from methemoglobinaemia.	**E] Hemodialysis or Hemoperfusion** - In severe cases **Symptomatic** 1. Arrhythmias → **verapamil & BB** 2. Seizures(difficult to manage) 1st by **diazepam** if no response, **phenobarbital** and if no response use **Na thiopental** *3.* Hypokalaemia **must not be aggressively treated** *because redistribution of K$^+$ occurs with decrease of theophylline level*